1: Hum Mol Genet. 2002 Jul 15;11(15):1687-96.

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PTEN blocks insulin-mediated ETS-2 phosphorylation through MAP kinase, independently of the phosphoinositide 3-kinase pathway.

Weng LP, Brown JL, Baker KM, Ostrowski MC, Eng C.

Clinical Cancer Genetics Program and Human Cancer Genetics Program, Division of Human Cancer Genetics, Department of Molecular Virology, Immunology and Medical Genetics, and Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210, USA.

The tumor suppressor PTEN possesses lipid and protein phosphatase activities. It has been well established that the lipid phosphatase activity is essential for its tumor-suppressive function via the phosphoinositide 3-kinase (PI3K) and Akt pathways. The precise role of the protein phosphatase activity is still unclear. In the current study, we demonstrate that overexpression of wild-type PTEN in the MCF-7 breast cancer line results in phosphatase activity-dependent decreases in the phosphorylation of ETS-2, which is a transcription factor whose DNA-binding ability is controlled by phosphorylation. Exposure of MCF-7 cells to insulin, insulin-like growth factor 1 (IGF-1) or epidermal growth factor (EGF) can lead to the phosphorylation of ETS-2, Akt and ERK1/2. The MEK inhibitor PD590089 abrogates insulin-stimulated phosphorylation of ETS-2. In contrast, the PI3K inhibitor LY492002 has no effect on insulin-stimulated phosphorylation of ETS-2, despite the fact that it diminishes insulin-stimulated phosphorylation of Akt. Interestingly, overexpression of PTEN in MCF-7 leads to blockade of insulin-stimulated, but not EGF-stimulated, phosphorylation of ERK, accompanied by dramatic decreases in ETS-2 phosphorylation. We further show that the relationship of PTEN and ETS-2 has functional significance by demonstrating that PTEN abrogates activation of the uPA Ras-responsive enhancer, a target of ETS-2 action, in a phosphatase-dependent manner, irrespective of the presence or absence of insulin. Our observations, therefore, suggest that PTEN blocks insulin-stimulated ETS-2 phosphorylation through inhibition of the ERK members of the MAP kinase family independently of PI3K, and that the PTEN effect on the phosphorylation status of ETS-2 may be mediated through PTEN's protein phosphatase activity.

PMID: 12095911 [PubMed - indexed for MEDLINE]

1: Blood. 2000 Nov 15;96(10):3560-8.

Related Articles, Links

Loss of PTEN expression leading to high Akt activation in human multiple myelomas.

Hyun T, Yam A, Pece S, Xie X, Zhang J, Miki T, Gutkind JS, Li W.

Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, MD, USA.

Mouse plasma cell tumor (PCT) and human multiple myeloma (MM) are terminal B-cell malignancies sharing many similarities. Our recent work demonstrated that activation of the insulin-like growth factor receptor (IGF-IR)/insulin receptor substrate (IRS)/phosphatidylinositol 3' kinase (PI 3'K) pathway was evident in the tumor lines derived from both species. Although PI 3'K activity was higher in mouse tumor lines than that in human tumors, activation of Akt serine/threonine kinase was markedly lower in mouse lines. This discrepancy prompted us to test the status of PTEN tumor suppressor gene, as it has been shown to be a negative regulator of PI 3'K activity. Although all the mouse lines expressed intact PTEN, 2 of the 4 human lines (Delta47 and OPM2) possessing the highest Akt activity lost PTEN expression. Sequencing analysis demonstrated that the PTEN gene contains a deletion spacing from exon 3 to exon 5 or 6 in the Delta47 line and from exon 3 to 7 in the OPM2 line. Restoration of PTEN expression suppressed IGF-I-induced Akt activity, suggesting that loss of PTEN is responsible for uncontrolled Akt activity in these 2 lines. Despite the expression of PTEN with the concomitant low Akt activity in all mouse PCT lines, their p70S6K activities were generally higher than those in 3 human MM lines, arguing for specific negative regulation of Akt, but not p70S6K by PTEN. These results suggest that p70S6K and Akt may be differentially used by the plasma cell tumors derived from mice and humans, respectively.

PMID: 11071655 [PubMed - indexed for MEDLINE]

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1: FEBS Lett. 2003 Jun 19;545(2-3):203-8.

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PTEN modulates insulin-like growth factor II (IGF-II)-mediated signaling; the protein phosphatase activity of PTEN downregulates IGF-II expression in hepatoma cells.

Kang-Park S, Lee YI, Lee YI.

Liver Cell Signal Transduction Laboratory, Bioscience Research Division, Korea Research Institute of Bioscience and Biotechnology, 305-606, Taejon, South Korea.

The PTEN gene (phosphatase and tensin homologous on chromosome 10) is frequently mutated or deleted in a number of malignancies including human hepatocellular carcinoma (HCC). We reported previously that the hepatitis B virus X (HBx) protein, known to be a causative agent in the formation of HCC, activates insulin-like growth factor II (IGF-II) expression through Sp1 phosphorylation by protein kinase C (PKC) or mitogen-activated protein kinase (MAPK) signaling. In this report we demonstrate that the PTEN effect on HBx induced IGF-II activation in a hepatoma cell line. Expression of PTEN and IGF-II was inversely related in different hepatoma cell lines. PTEN expression induced decreased Sp1 DNA binding by dephosphorylating Sp1 and interfered with transcriptional transactivation of IGF-II by HBx in hepatoma cells. The protein phosphatase activity was involved in PTEN downregulation of IGF-II transcription through downregulation of MAPK, MAPK kinase phosphorylation and PKC translocation. Our data suggest that PTEN blocks Sp1 phosphorylation in response to HBx, by inactivating PKC, MAPK and MAPK kinase which eventually downregulate IGF-II expression, during the formation of HCC.

PMID: 12804776 [PubMed - in process]

1: Endocrinology. 2000 Jun;141(6):1930-5.

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Persistent activation of phosphatidylinositol 3-kinase causes insulin resistance due to accelerated insulin-induced insulin receptor substrate-1 degradation in 3T3-L1 adipocytes.

Egawa K, Nakashima N, Sharma PM, Maegawa H, Nagai Y, Kashiwagi A, Kikkawa R, Olefsky JM.

Department of Medicine, University of California, San Diego, La Jolla 92093-0673, USA.

Recently, we have reported that the overexpression of a membrane-targeted phosphatidylinositol (PI) 3-kinase (p110CAAX) stimulated p70S6 kinase, Akt, glucose transport, and Ras activation in the absence of insulin but inhibited insulin-stimulated glycogen synthase activation and MAP kinase phosphorylation in 3T3-L1 adipocytes. To investigate the mechanism of p110CAAX-induced cellular insulin resistance, we have now studied the effect of p110CAAX on insulin receptor substrate (IRS)-1 protein. Overexpression of p110CAAX alone decreased IRS-1 protein levels to 63+/-10% of control values. Insulin treatment led to an IRS-1 gel mobility shift (most likely caused by serine/threonine phosphorylation), with subsequent IRS-1 degradation. Moreover, insulin-induced IRS-1 degradation was enhanced by expression of p110CAAX (61+/-16% vs. 13+/-15% at 20 min, and 80+/-8% vs. 41+/-12% at 60 min, after insulin stimulation with or without p110CAAX expression, respectively). In accordance with the decreased IRS-1 protein, the insulin-stimulated association between IRS-1 and the p85 subunit of PI 3-kinase was also decreased in the p110CAAX-expressing cells, and IRS-1-associated PI 3-kinase activity was decreased despite the fact that total PI 3-kinase activity was increased. Five hours of wortmannin pretreatment inhibited both serine/threonine phosphorylation and degradation of IRS-1 protein. These results indicate that insulin treatment leads to serine/threonine phosphorylation of IRS-1, with subsequent IRS-1 degradation, through a PI 3-kinase-sensitive mechanism. Consistent with this, activated PI 3-kinase phosphorylates IRS-1 on serine/threonine residues, leading to IRS- 1 degradation. The similar finding was observed in IRS-2 as well as IRS-1. These results may also explain the cellular insulin-resistant state induced by chronic p110CAAX expression.

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1: Proc Natl Acad Sci U S A. 2001 Apr 10;98(8):4640-5. Epub 2001 Apr 03.

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A phosphatidylinositol 3-kinase/Akt/mTOR pathway mediates and PTEN antagonizes tumor necrosis factor inhibition of insulin signaling through insulin receptor substrate-1.

Ozes ON, Akca H, Mayo LD, Gustin JA, Maehama T, Dixon JE, Donner DB.

Department of Microbiology and Immunology, Indiana University School of Medicine and the Walther Oncology Center, Indianapolis, IN 46202, USA.

Tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) by the insulin receptor permits this docking protein to interact with signaling proteins that promote insulin action. Serine phosphorylation uncouples IRS-1 from the insulin receptor, thereby inhibiting its tyrosine phosphorylation and insulin signaling. For this reason, there is great interest in identifying serine/threonine kinases for which IRS-1 is a substrate. Tumor necrosis factor (TNF) inhibited insulin-promoted tyrosine phosphorylation of IRS-1 and activated the Akt/protein kinase B serine-threonine kinase, a downstream target for phosphatidylinositol 3-kinase (PI 3-kinase). The effect of TNF on insulin-promoted tyrosine phosphorylation of IRS-1 was blocked by inhibition of PI 3-kinase and the PTEN tumor suppressor, which dephosphorylates the lipids that mediate PI 3-kinase functions, whereas constitutively active Akt impaired insulin-promoted IRS-1 tyrosine phosphorylation. Conversely, TNF inhibition of IRS-1 tyrosine phosphorylation was blocked by kinase dead Akt. Inhibition of IRS-1 tyrosine phosphorylation by TNF was blocked by rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR), a downstream target of Akt. mTOR induced the serine phosphorylation of IRS-1 (Ser-636/639), and such phosphorylation was inhibited by rapamycin. These results suggest that TNF impairs insulin signaling through IRS-1 by activation of a PI 3-kinase/Akt/mTOR pathway, which is antagonized by PTEN.

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1: Mol Cell Biol. 2001 Jun;21(12):3947-58.

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PTEN expression causes feedback upregulation of insulin receptor substrate 2.

Simpson L, Li J, Liaw D, Hennessy I, Oliner J, Christians F, Parsons R.

Institute of Cancer Genetics, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.

PTEN is a tumor suppressor that antagonizes phosphatidylinositol-3 kinase (PI3K) by dephosphorylating the D3 position of phosphatidylinositol (3,4,5)-triphosphate (PtdIns-3,4,5-P3). Given the importance of PTEN in regulating PtdIns-3,4,5-P3 levels, we used Affymetrix GeneChip arrays to identify genes regulated by PTEN. PTEN expression rapidly reduced the activity of Akt, which was followed by a G(1) arrest and eventually apoptosis. The gene encoding insulin receptor substrate 2 (IRS-2), a mediator of insulin signaling, was found to be the most induced gene at all time points. A PI3K-specific inhibitor, LY294002, also upregulated IRS-2, providing evidence that it was the suppression of the PI3K pathway that was responsible for the message upregulation. In addition, PTEN, LY294002, and rapamycin, an inhibitor of mammalian target of rapamycin, caused a reduction in the molecular weight of IRS-2 and an increase in the association of IRS-2 with PI3K. Apparently, PTEN inhibits a negative regulator of IRS-2 to upregulate the IRS-2-PI3K interaction. These studies suggest that PtdIns-3,4,5-P3 levels regulate the specific activity and amount of IRS-2 available for insulin signaling.

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1: Mol Endocrinol. 2001 Aug;15(8):1411-22.

Related Articles, Links

Regulation of phosphoinositide metabolism, Akt phosphorylation, and glucose transport by PTEN (phosphatase and tensin homolog deleted on chromosome 10) in 3T3-L1 adipocytes.

Ono H, Katagiri H, Funaki M, Anai M, Inukai K, Fukushima Y, Sakoda H, Ogihara T, Onishi Y, Fujishiro M, Kikuchi M, Oka Y, Asano T.

Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo 113, Japan.

To investigate the roles of PTEN (phosphatase and tensin homolog deleted on chromosome 10) in the regulation of 3-position phosphorylated phosphoinositide metabolism as well as insulin-induced Akt phosphorylation and glucose metabolism, wild-type PTEN and its phosphatase-dead mutant (C124S) with or without an N-terminal myristoylation tag were overexpressed in Sf-9 cells and 3T3-L1 adipocytes using baculovirus and adenovirus systems, respectively. When expressed in Sf-9 cells together with the p110alpha catalytic subunit of phosphoinositide 3-kinase, myristoylated PTEN markedly reduced the accumulations of both phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate induced by p110alpha. In contrast, overexpression of the C124S mutants apparently increased these accumulations. In 3T3-L1 adipocytes, insulin-induced accumulations of phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate were markedly suppressed by overexpression of wild-type PTEN with the N-terminal myristoylation tag, but not by that without the tag. On the contrary, the C124S mutants of PTEN enhanced insulin-induced accumulations of phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate. Interestingly, the phosphorylation level of Akt at Thr308 (Akt2 at Thr309), but not at Ser473 (Akt2 at Ser474), was revealed to correlate well with the accumulation of phosphatidylinositol 3,4,5-trisphosphate modified by overexpression of these PTEN proteins. Finally, insulin-induced increases in glucose transport activity were significantly inhibited by the overexpression of myristoylated wild-type PTEN, but were not enhanced by expression of the C124S mutant of PTEN. Therefore, in conclusion, 1) PTEN dephosphorylates both phosphatidylinositol 3,4-bisphosphate and phosphatidylinositol 3,4,5-trisphosphate in vivo, and the C124S mutants interrupt endogenous PTEN activity in a dominant-negative manner. 2) The membrane targeting process of PTEN may be important for exerting its function. 3) Phosphorylations of Thr309 and Ser474 of Akt2 are regulated differently, and the former is regulated very sensitively by the function of PTEN. 4) The phosphorylation level of Ser474, but not that of Thr309, in Akt2 correlates well with insulin-stimulated glucose transport activity in 3T3-L1 adipocytes. 5) The activity of endogenous PTEN may not play a major role in the regulation of glucose transport activity in 3T3-L1 adipocytes.

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1: Diabetes. 2002 Apr;51(4):1028-34.

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Specific inhibition of PTEN expression reverses hyperglycemia in diabetic mice.

Butler M, McKay RA, Popoff IJ, Gaarde WA, Witchell D, Murray SF, Dean NM, Bhanot S, Monia BP.

Isis Pharmaceuticals, Carlsbad, California 92008, USA.

Signaling through the phosphatidylinositol 3'-kinase (PI3K) pathway is crucial for metabolic responses to insulin, and defects in PI3K signaling have been demonstrated in type 2 diabetes. PTEN (MMAC1) is a lipid/protein phosphatase that can negatively regulate the PI3K pathway by dephosphorylating phosphatidylinositol (3,4,5)-triphosphate, but it is unclear whether PTEN is physiologically relevant to insulin signaling in vivo. We employed an antisense oligonucleotide (ASO) strategy in an effort to specifically inhibit the expression of PTEN. Transfection of cells in culture with ASO targeting PTEN reduced PTEN mRNA and protein levels and increased insulin-stimulated Akt phosphorylation in alpha-mouse liver-12 (AML12) cells. Systemic administration of PTEN ASO once a week in mice suppressed PTEN mRNA and protein expression in liver and fat by up to 90 and 75%, respectively, and normalized blood glucose concentrations in db/db and ob/ob mice. Inhibition of PTEN expression also dramatically reduced insulin concentrations in ob/ob mice, improved the performance of db/db mice during insulin tolerance tests, and increased Akt phosphorylation in liver in response to insulin. These results suggest that PTEN plays a significant role in regulating glucose metabolism in vivo by negatively regulating insulin signaling.

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1: J Cell Biol. 2001 Dec 24;155(7):1129-35. Related Articles, Lin

The lipid phosphatase activity of PTEN is critical for stabilizing intercellular junctions and reverting invasiveness.

Kotelevets L, van Hengel J, Bruyneel E, Mareel M, van Roy F, Chastre J

Institut National de la Sante et de la Recherche Medicale (INSERM) U410, Faculte de Medecine Bichat, 75018 Paris, France.

To analyze the implication of PTEN in the control of tumor cell invasiveness the canine kidney epithelial cell lines MDCKras-f and MDCKts-src, expressing activated Ras and a temperature-sensitive v-Src tyrosine kinase, respectively, were transfected with PTEN expression vectors. Likewise, the human PTEN-defective glioblastoma cell lines U87MG and U373MG, the melanoma cell line FM-45, and the prostate carcinoma cell line PC-3 were transfected. We demonstrate that ectopic expression of wild-type PTEN in MDCKts-src cells, but not expression of PTEN mutants deficient in either th lipid or both the lipid and protein phosphatase activities, reverted the morphological transformation, induced cell-cell aggregation, and suppressed the invasive phenotype in an E-cadherin-dependent manner. In contrast, overexpression of wild-type PTEN did not counteract Ras-induced invasiveness of MDCKras-f cells expressing low levels of E-cadherin. PTEN effects were not associated with marked changes in accumulation or phosphorylation levels of E-cadherin and associated catenins. Wild-type, but not mutant, PTEN also reverted the invasive phenotype of U87MG, U373MG PC-3, and FM-45 cells. Interestingly, PTEN effects were mimicked by N-cadherin-neutralizing antibody in the glioblastoma cell lines. Our data confirm the differential activities of E- and N-cadherin on invasiveness and suggest that the lipid phosphatase activity of PTEN exerts a critical role in stabilizing junctional complexes and restraining invasiveness.

PMID: 11756467 [PubMed - indexed for MEDLINE]

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1: J Clin Invest. 2002 Sep;110(6):815-25.

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PTEN overexpression suppresses proliferation and differentiation and enhances apoptosis of the mouse mammary epithelium.

Dupont J, Renou JP, Shani M, Hennighausen L, LeRoith D.

Section on Molecular and Cellular Physiology, Clinical Endocrinology Branch, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, Maryland 20892, USA.

The phosphatase PTEN regulates growth, adhesion, and apoptosis, among many other cell processes. To investigate its role during mouse mammary gland development, we generated MK-PTEN, a transgenic mouse model in which human PTEN is overexpressed in ductal and alveolar mammary epithelium during puberty, pregnancy, lactation, and involution. No obvious phenotype was observed in mammary tissue of pubescent virgin mice. However, MK-PTEN females could not lactate normally, and approximately 30% of pups died, with survivors exhibiting growth retardation. Transgenic offspring nursed by wild-type foster mothers, conversely, developed normally. This phenotype is consistent with a reduced number of alveolar epithelial cells due to a decrease in cell proliferation and an increase in apoptosis. Using mammary-enriched cDNA microarrays, we identified several genes that were preferentially expressed in MK-PTEN mammary tissue, including the IGF-binding protein-5 (Igfbp5) gene, and others whose expression was reduced, including the genes for c-Jun amino-terminal kinase. Secretory epithelial cell differentiation was impaired, as measured by the expression of specific milk protein genes. MK-PTEN mice also exhibited a 50% decrease in the phosphorylation state of Akt. Taken together, these results suggest that PTEN controls mammary gland development and, consequently, lactation.

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1: Front Biosci. 2002 May 1;7:e245-51.

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Biological role of phosphatase PTEN in cancer and tissue injury healing.

Tsugawa K, Jones MK, Sugimachi K, Sarfeh IJ, Tarnawski AS.

Department of Medicine, Department of Veterans Affairs Medical Center, Long Beach, California 90822, USA.

PTEN (phosphatase and tensin homolog deleted on chromosome ten) also referred to as MMAC (mutated in multiple advanced cancers) was discovered as a tumor suppressor gene and later found to be a phospholipid phosphatase. PTEN negatively regulates Akt activation by preventing its phosphorylation. PTEN therefore inhibits the PI 3-kinase/Akt signaling pathway which is important for cell growth and survival. Overexpression or enhanced activation of PTEN can potentially impair injury healing by at least 4 mechanisms. PTEN can: 1) inhibit entry into the cell cycle by inhibiting G1 to S phase progression and arrest cell proliferation required for tissue reconstruction during injury healing; 2) increase apoptosis by blocking Akt activation leading to increased Bad and Caspase-9 activities; 3) inhibit hypoxia-induced angiogenesis required for injury healing by blocking Akt-mediated VEGF gene transcription; 4) inhibit Akt-mediated cell migration, i.e. re-epithelialization, which is also required for injury healing. The same mechanisms can also suppress cancer growth and metastases. Therefore, elucidating the role of the PTEN/PI 3-kinase/Akt pathway will likely advance our knowledge of the mechanisms controlling the processes of injury healing and cancer growth.

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1: Hum Mol Genet. 2001 Feb 1;10(3):237-42.

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PTEN induces apoptosis and cell cycle arrest through phosphoinositol-3-kinase/Akt-dependent and -independent pathways.

Weng L, Brown J, Eng C.

Clinical Cancer Genetics and Human Cancer Genetics Programs, Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210, USA.

The tumour suppressor PTEN inhibits cell growth through multiple mechanisms. We have previously demonstrated that overexpression of PTEN in MCF-7 breast cancer cells causes G(1) arrest followed by cell death, the latter of which is believed to be mediated by the phosphoinositol-3-kinase (PI3K) and Akt/PKB pro-apoptotic pathways. In this present study, we show that culture in the presence of low levels of growth factors increased PTEN-mediated growth suppression through the enhancement of PTEN-induced cell death. The caspase 9-specific inhibitor, ZVAD, blocked PTEN-induced cell death without altering the effect of PTEN on cell cycle distribution. Depending on the level of expression, overexpression of dominant-negative Akt induces more cell death and has less effect on the cell cycle or induces similar or decreased cell death without affecting the cell cycle compared with effects on cell death and the cell cycle when overexpressing PTEN. These observations in sum suggest that, in MCF-7 breast cancer cells, the apoptotic cells induced by the overexpression of PTEN did not derive from the G(1)-arrested cells. Further, the effect of PTEN on cell death is mediated through the PI3K/Akt pathway whereas PTEN-mediated cell cycle arrests are through PI3K/Akt-dependent and -independent pathways.

PMID: 11159942 [PubMed - indexed for MEDLINE]

1: Cancer Res. 1999 Dec 15;59(24):6063-7.

Related Articles, Links

Growth suppression of human ovarian cancer cells by adenovirus-mediated transfer of the PTEN gene.

Minaguchi T, Mori T, Kanamori Y, Matsushima M, Yoshikawa H, Taketani Y, Nakamura Y.

Laboratory of Molecular Medicine, Human Genome Center, The Institute of Medical Science, The University of Tokyo, Japan.

A tumor suppressor gene on chromosome 10q23, PTEN, encodes a phosphatidylinositol phosphatase that antagonizes activation of the phosphatidylinositol 3'-kinase-mediated pathway involved in cell growth. A gene encoding the catalytic subunit of phosphatidylinositol 3'-kinase (PIK3CA) is frequently activated in ovarian cancers; therefore, overexpression of the PTEN product through gene transfer might be an effective strategy for treating ovarian cancers. To test the potential for this type of gene therapy, we constructed a recombinant adenovirus encoding wild-type PTEN and examined its effects on nine cell lines derived from human ovarian carcinomas. Transduction of the PTEN gene significantly inhibited growth of six of these cell lines compared with infection with virus alone, and the degree of inhibition correlated with the efficiency of gene transfer as determined by beta-galactosidase assay. Results of flow cytometry suggested that the observed effects were mediated by two mechanisms, apoptosis and/or arrest in the G1 phase of the cell cycle, and that high adenoviral transduction efficiency of cells was associated with induction of apoptosis. We also found that the level of transcription of Integrin alpha(v) in ovarian cancer cells correlated with the efficiency of transduction ($P = 0.014$) and with the degree of growth inhibition after PTEN gene transfer ($P = 0.009$). These findings carry significant implications for adenovirus vector-based PTEN gene therapies for ovarian cancers.

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1: Clin Cancer Res. 2002 May;8(5):1248-52.

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Overexpression of PTEN increases sensitivity to SN-38, an active metabolite of the topoisomerase I inhibitor irinotecan, in ovarian cancer cells.

Saga Y, Mizukami H, Suzuki M, Kohno T, Urabe M, Ozawa K, Sato I.

Department of Obstetrics and Gynecology, Jichi Medical School, Yakushiji, Minamikawachi, Tochigi 329-0498, Japan. saga@jichi.ac.jp

PURPOSE: PTEN is a tumor suppressor gene that was identified on chromosome 10q23. In addition to its original function as a tumor suppressor, this gene product was recently reported to enhance the sensitivity of cancer cells to anticancer agents. It is for the purpose of this study to investigate its function and the mechanisms by which PTEN enhances the sensitivity of ovarian cancer to antitumor agents. EXPERIMENTAL DESIGN: PTEN cDNA was introduced into the ovarian cancer cell line SHIN-3 and a high-expression cell line (SHIN-3/PTEN) was established. This cell line and a control were further analyzed. RESULTS: SHIN-3 cells did not carry any mutations in its genome after sequencing. In vitro examination of sensitivity to anticancer agents showed that the 50% growth-inhibitory concentration value for irinotecan metabolite (SN-38) in SHIN-3/PTEN was 800 nM, a 6.6-fold higher sensitivity compared with that of the control (5300 nM). There were no differences in sensitivity to cisplatin, paclitaxel, or gemcitabine between SHIN-3/PTEN and the controls. The percentage of apoptotic cells in SHIN-3/PTEN was 16.6 +/- 0.7% 24 h after addition of SN-38, a significant increase over controls (8.6 +/- 0.9%; $P < 0.01$). Lower topoisomerase I activity was observed in SHIN-3/PTEN, compared with controls. CONCLUSIONS: These results indicate that high PTEN expression enhances the sensitivity of ovarian cancer cells to irinotecan and the induction of apoptosis and the suppression of topoisomerase I activity in cancer cells are suggested as possible mechanisms attributable to high PTEN expression.

PMID: 12006545 [PubMed - indexed for MEDLINE]

1: Cancer. 2003 Apr 15;97(8):1929-40.

Related Articles, Links

Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEP1 in hepatocellular carcinoma.

Hu TH, Huang CC, Lin PR, Chang HW, Ger LP, Lin YW, Changchien CS, Lee CM, Tai MH.

Division of Hepatology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

BACKGROUND: Inactivation of the tumor suppressor gene PTEN/MMAC1/TEP1, located on chromosome 10q23, is a common event in advanced stages of diverse human malignancies. However, the prognostic role of PTEN expression in patients with hepatocellular carcinoma (HCC) has not been characterized. METHODS: One hundred five resected specimens were collected from patients with HCC. Expression levels of PTEN and p53 in clinical samples were analyzed by immunohistochemistry. RESULTS: Immunohistochemical analysis of 105 HCC tissue specimens revealed that decreased or absence of PTEN immunostaining was found in 43 specimens (40.9%). Reduced PTEN expression levels were correlated with increased tumor grade (P = 0.017), advanced disease stage (P = 0.016), and elevated serum alpha-fetoprotein (alphaFP) levels (P = 0.001). Kaplan-Meier analysis indicated that patients with reduced PTEN levels had shorter overall survival (P = 0.001) and higher recurrence rates (P = 0.0007) compared with patients who had intact PTEN expression. Examining p53 expression unveiled an inverse correlation between p53 overexpression and reduced PTEN expression in patients with HCC (P = 0.004). In addition, patients with p53 overexpression had shorter overall survival compared with patients who were without p53 overexpression (P = 0.0014). Univariate and multivariate analyses revealed that reduced PTEN expression was an independent prognostic factor for survival in patients with HCC. CONCLUSIONS: The current study demonstrated that reduced PTEN expression levels are involved in the pathogenesis of HCC. Moreover, decreased PTEN expression was correlated with tumor progression, high alphaFP levels, p53 overexpression, and poor prognosis in patients with HCC. Copyright 2003 American Cancer Society.

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19. Sun, H., Charles, C. H., Lau, L. F. & Tonks, N. K. (1993) *Cell* **75,** 487–493.
20. Garton, A. J., Flint, A. J. & Tonks, N. K. (1996) *Mol. Cell. Biol.* **16,** 6408–6418.
21. Bos, J. L. (1995) *Trends Biochem. Sci.* **20,** 441–442.
22. Marte, B. M. & Downward, J. (1997) *Trends Biochem. Sci.* **22,** 355–358.
23. Datta, S. R., Dudek, H., Tao, X., Masters, S., Fu, H., Gotoh, Y. & Greenberg, M. E. (1997) *Cell* **91,** 231–241.
24. Andjelkovic, M., Alessi, D. R., Meier, R., Fernandez, A., Lamb, N. J., Frech, M., Cron, P., Cohen, P., Lucocq, J. M. & Hemmings, B. A. (1997) *J. Biol. Chem.* **272,** 31515–31524.
25. Risinger, J. I., Hayes, A. K., Berchuck, A. & Barrett, J. C. (1997) *Cancer Res.* **57,** 4736–4738.
26. Cairns, P., Okami, K., Halachmi, S., Halachmi, N., Esteller, M.,
27. Wang, S. I., Puc, J., Li, J., Bruce, J. N., Cairns, P., Sidransky, D. & Parsons, R. (1997) *Cancer Res.* **57,** 4183–4186.
28. Tashiro, H., Blazes, M. S., Wu, R., Cho, K. R., Bose, S., Wang, S. I., Li, J., Parsons, R. & Ellenson, L. H. (1997) *Cancer Res.* **57,** 3935–3940.
29. Alessi, D. R., James, S. R., Downes, C. P., Holmes, A. B., Gaffney, P. R., Reese, C. B. & Cohen, P. (1997) *Curr. Biol.* **7,** 261–269.
31. Toker, A. & Cantley, L. C. (1997) *Nature (London)* **387,** 673–676.
32. Bellacosa, A., Testa, J. R., Staal, S. P. & Tsichlis, P. N. (1991) *Science* **254,** 274–277.
33. Chang, H. W., Aoki, M., Fruman, D., Auger, K. R., Bellacosa, A., Tsichlis, P. N., Cantley, L. C., Roberts, T. M. & Vogt, P. K. (1997) *Science* **276,** 1848–1850.